A Call to Action for Acute Lymphoblastic Leukemia
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The cure rates for precursor B-cell acute lymphoblastic leukemia (ALL) among children have improved, but the prognosis for older patients and children with relapsed disease remains poor. Risk stratification based on clinical features and disease characteristics can improve outcomes by enabling physicians to reduce the toxicity of therapy for patients with lower-risk disease and intensify therapy for patients with higher-risk disease. The negative prognosis associated with the t(9;22) translocation, which results in expression of the BCR-ABL1 activated kinase fusion protein, is attenuated by treatment that includes tyrosine kinase inhibitors, providing a paradigm for molecularly guided therapy in patients with precursor B-cell ALL. Several years ago, a subtype of precursor B-cell ALL was identified that shares a gene-expression profile with Ph-positive ALL (the term commonly used to describe ALL associated with the Philadelphia chromosome, which results from the t(9;22) translocation).1,2 The pattern of gene expression in patients with Ph-like ALL prompted the hypothesis that other oncogenic drivers could substitute for BCR-ABL1, triggering a similar signaling cascade. Indeed, previous studies have identified rearrangements and mutations that activate cytokine receptor signaling in some cases of Ph-like ALL.3,4

In this issue of the Journal, Roberts et al.5 define the frequency and genomic landscape of Ph-like ALL in a cohort of 1725 children and young adults with precursor B-cell ALL. They observed a marked rise in the proportion of Ph-like cases with age, from 12% among children to 27% among young adults (Fig. 1A). Nearly half (49.4%) of the young adults had either Ph-positive or Ph-like disease. The Ph-like cases were frequently found to be associated with IKZF1 alterations (in 68% of patients with Ph-like ALL) and high CRLF2 expression (in 47%), with the latter caused by genomic rearrangement in all

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patients examined — findings that are consistent with the results of previous studies. Patients with high CRLF2 expression frequently had JAK1 or JAK2 mutations (found in 55% of patients with CRLF2 rearrangement), as previously reported, but the study by Roberts et al. extends these findings considerably. Comprehensive genomic analysis revealed somatic mutations (fusion, deletions, or point mutations) predicted to alter kinase activity in 91% of patients with Ph-like ALL. (The remaining patients did not have a kinase-altering mutation or had insufficient material available for analysis.) A majority of the mutations affected cytokine receptors (e.g., EPOR, FLT3, or PDGFRB) or their downstream signaling pathways (Fig. 1B). Several of the mutant alleles had functional consequences when ectopically expressed in cell lines (conferring cytokine independence or constitutive STAT5 activation). The growth and aberrant signaling in these cell lines were inhibited in a predictable fashion: fusions involving ABL1,

Figure 1. Actionable Genetic Lesions in Philadelphia Chromosome–like (Ph-like) Precursor B-Cell Acute Lymphoblastic Leukemia (ALL).
Panel A shows the distribution of major molecular subtypes of precursor B-cell ALL. The proportion of cases associated with an unfavorable prognosis (e.g., Ph-positive [BCR–ABL1] or Ph-like ALL) increases from childhood (1 to 15 years of age) to adolescence (16 to 20 years of age) and young adulthood (21 to 39 years of age), and the proportion of cases with a more favorable prognosis (e.g., hyperdiploidy or ETV6–RUNX1) decreases with age. Percentages may not sum to 100 because of rounding. Panel B shows the heterodimeric thymic stromal lymphopoietin receptor (TSLPR) complex that signals through the JAK–STAT pathway to regulate B-cell lymphopoiesis, among other functions. Kinase-activating mutations in this and other cytokine signaling pathways are frequent in precursor B-cell ALL and represent potential therapeutic targets of kinase inhibitors. P denotes a phosphate group.
tyrosine kinase inhibitors in the management of ALL in adults require additional study, with the possibility that the poor prognosis for adults may be due in part to a higher prevalence of this disability that the potential prognostic and therapeutic significance of the Ph-like subtype mandates development of diagnostic tools that can be widely deployed. Gene-expression profiling remains a research technique that is not practical for routine use in diagnostic laboratories. Low-density gene-expression arrays or flow cytometry–based assays have been proposed as alternative diagnostic strategies, but these methods require further refinement and validation. Finally, rapid-turnaround molecular profiling will be needed to identify potentially actionable mutations in patients with Ph-like ALL. Mutational profiling with the use of large gene panels is now widely available in academic centers and commercial laboratories, but many of these platforms do not include a strategy for gene-fusion detection.

Improvements in risk stratification and tailored treatment plans for children with precursor B-cell ALL represent major successes in pediatric oncology. The findings of Roberts et al. provide new opportunities for investigation in children and young adults with Ph-like ALL and may well be extended to address the unmet medical needs of older adults with precursor B-cell ALL.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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